In the Abstract:

At page 134, line 3, please remove "An Aiolos protein" and replace with –The invention features an Aiolos protein, and nucleic acid sequence encoding such protein. The invention also features methods of making and using an Aiolos protein, and methods of obtaining an antibody from an animal having an Aiolos deregulated cell.--

REMARKS

Claims 18-41 are pending in the present application. Claim 42 has been cancelled, without prejudice. Claims 18, 23, 29 and 33-35 have been amended. However, the amendment to and/or the cancellation of the claims have been made solely to expedite prosecution of the present application. Applicants have also amended the abstract and the specification. No new matter has been added.

Rejection of Claims 18-41 Under 35 U.S.C. §112, second paragraph

Claims 18-41 are rejected under 35 U.S.C. §112, first paragraph, 'as being indefinite for failing to particularly point out and distinctly claim the subject matter the applicant regards as the invention." In particular, the Examiner states that

Claims 18, 29 and 35 are unclear because of the recitation of the term 'a method of providing an antibody'. The claim would read more clearly if it recited a method of making or a method of isolating an antibody."

Claims 18, 29 and 35 have been amended to recite a method of obtaining an antibody, thereby obviating the Examiner's rejection to these claims.

Claims 24 and 34 are rejected by the Examiner as "lacking antecedent basis for the term 'antigen'." Claims 24 and 34 have been amended, thereby obviating the Examiner's rejection of these claims.

The Examiner further rejected claim 18, stating that

> it is unclear what the term 'mammal having a cell which is Aiolos deregulated' means. Is the term limited to animals which have a mutation or deletion in the gene encoding Aiolos protein which results in Aiolos protein with abnormal function? Does the term encompass animals in which Aiolos gene is deregulated but the gene encoding Aiolos protein is wild type?

Applicants respectfully traverse this rejection. Page 46, lines 10-18 of the present application states that "an Aiolos deregulated animal is an animal in which the physiological function of the Aiolos protein is inhibited and deregulated B cell responses, e.g., production of autoantibodies, are manifested." Applicants also provide examples of ways in which the physiological function of Aiolos can be inhibited. Thus, the meaning of the term "mammal having a cell which is Aiolos deregulated" as recited in claim 18 is clear.

For the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of Claims 24 and 34 Under 35 U.S.C. §112, first paragraph

Claims 24 and 34 are rejected under 35 U.S.C. §112, first paragraph, as "not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims." According to the Examiner,

> [i]t is unpredictable what proteins are homologous with eachother because the specification does not give guidance as to how to determine if a protein is homologous with another protein. The specification does not disclose any algorithm for sequence analysis to determine if two proteins are homologous. There is no guidance in the specification as to what allowances to use for gaps and insertions or what weighing factors are given for conservative substitutions. Therefore one with skill in the art would not to be able to obtain an antibody to an antigen that is at least 90% homologous to an antigen because one with skill in the art would not be able to determine if two antigens are at least 90% homologous.

Applicants respectfully traverse this rejection. There is clearly sufficient guidance in the present application for a skilled artisan to determine if two antigens are homologous with each other. At page 43, lines 22-37 and page 44, lines 1-11 of the present application, Applicants provide methods of determining the percent homology of two amino acid sequences. For example, page 44, lines 6-11 of the present application provides that the mathematical algorithm of Myers and Miller, CABIOS (1989) can be utilized to compare amino acid sequences and that this algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. In addition, Applicants provide that when utilizing the ALIGN program for comparing amino acid sequence, a PAM120 weight residue table, a gap

length penalty of 12, and a gap penalty of 4 can be used. Thus, the present application clearly provides sufficient guidance for one of ordinary skill in the art to determine if an antigen is at least 90% homologous to a second antigen. Using this information, a skilled artisan could clearly use the claimed methods to obtain an antibody to an antigen that is at least 90% homologous to another antigen.

Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of Claims 18, 19, 22, 23, 25-29, 32, 33, 35, 36, 37, and 40-42 Under 35 U.S.C. §102(b)

Claims 18, 19, 22, 23, 25-29, 32, 33, 35, 36, 37, and 40-42 Under 35 U.S.C. §102(b) as being anticipated by Frosch et al. (1985) *PNAS USA* 82:1194. According to the Examiner,

> Frosch et al. teach a method of producing monoclonal antibodies by immunizing NZB mice with poorly antigenic antigen, K1 polysaccharide. Frosch et al. teach the K1 polysaccharide is poorly immunogenic in wild type mice, IE Balb/c mice (see abstract). Frosch et al. teach a method of obtaining a monoclonal antibody by immunizing mice with bacteria expressing K1 polysaccharide, isolating lymphocytes from the immunized mice and fusing the cells to produce hybridomas secreting anti-K1 antibodies (see page 1195, in particular). Frosch et al. teach that the antibody is an IgG antibody (see page 1195, in particular). Frosch et al. teach that NZB mice immunized with a weak antigen produced increased IgG response to antigens when compared to wild type (BALB/c) mice (see page 1197, in particular). Frosch et al. teach that NZB mice are known to exhibit hyperactivity of both its B-cell and T-cell system (see page 1197, in particular).
>
> Frosch et al. is silent as to whether NZB mice are also Aiolos deregulated or homozygous for null or under expressing mutations at the Aiolos locus. However, NZB mice have the same phenotype as Aiolos deregulated mice, IE they are hypersenstative in B cell and T cell compartment, have increased levels of autoantibodies and elevated IgG responses to antigens (see page 96 of the specification). Therefore, absent data to the contrary, the method of obtaining antibodies taught by Frosch et al. is the same as the instantly claimed method of obtaining antibodies.

Applicants respectfully traverse this rejection. The claims are directed to methods of obtaining an antibody which include providing a mammal having a cell which is Aiolos

deregulated or homozygous for null or under expressing mutations in Aiolos; and isolating an antibody from the animal or from a cell derived from the animal, to thereby obtain an antibody.

Frosch et al. discuss the production of monoclonal antibodies to weak antigens in NZB mice. Frosch et al. generally state that a humoral response may be more easily provoked in NZB mice strain which is known the exhibit hyperactivity of both its B-cell and T-cell systems. However, nowhere is Frosch et al. is there any teaching or suggestion that deregulation of Aiolos may provide an animal (or cell from the animal) which can be used to obtain antibodies. There is no mention whatsoever of Aiolos in the Frosch reference.

The Examiner speculates that because the NZB mice disclosed in Frosch et al. are hypersensitive to B-cell and T-cell compartment, have increased levels of autoantibodies and elevated IgG responses to antigens, these mice may be the same as the Aiolos deregulated mice described in the present application. However, just because there are similarities in the phenotypes of these animals does not mean that the same underlying mechanism is responsible. Throughout the present application, Applicants teach that deregulation of Aiolos leads to increased production and proliferation of B cells. In addition, Applicants provide that there is also a modest increase in the proliferative capacity of thymocytes and mature T cells. On the other hand, the phenotype of NZB mice has been attributed to deficiencies in T cell development. See e.g., Hashimoto et al. (2000) *J. Immunol.* 164(3):1569-1575, submitted herewith as Exhibit A. Since it has been shown that the phenotype of NZB mice is attributed to decreased T cell development, whereas mice having Aiolos deregulated cells show an increase in mature T cells (as well as B cells), the mechanism behind the production of antibodies from these two different mice is not the same. In addition, other differences between NZB mice and Aiolos deregulated mice include: 1) an increase in CD5 B cells found in NZB mice, whereas there is a decrease in Aiolos deregulated mice; and 2) there is a decrease with age of bone marrow B cells in NZB mice, whereas there is no age effect on these cells in Aiolos deregulated mice. Thus, it is clear that Frosch et al. do not teach or suggest obtaining antibodies from an Aiolos deregulated animal (or cell of such an animal).

> The antibody in claim 42 is anticipated by the antibody produced by Frosch et al. It is noted that the limitation wherein the antibody is produced by an Aiolos mutant animal or cell does not does not distinguish the antibody from prior art antibodies. The claims antibody is anticipated by prior art antibodies produced by another strain of mouse or animal.

Claim 42 has been cancelled, thereby obviating the Examiner's rejection to this claim.

For the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of Claims 18-19, 21-29, 31-37 and 39-42 are rejected under 35 U.S.C. §103(a)

Claims 18-19, 21-29, 31-37 and 39-42 are rejected under 35 U.S.C. §103(a) as being unpatentable over Frosch et al., supra. According to the Examiner,

> Frosch et al. have been discussed supra. The invention claimed in claims 21, 24, 34, 39 differs from the method of producing antibodies as taught by Frosch et al. because Frosch et al. does not obtain antibodies specific for autoantigens or for antigens which are 90% homologous to an endogenous antigen. However, based on the teachings of Frosch et al. who teaches that obtaining antibodies to weak antigens by immunizing NZB mice with such antigens, one of ordinary skill in the art would be motivated to obtain antibodies to any weak antigen, IE autoantigens or antigens that are highly homologous to self antigens, by immunizing NZB mice with such antigens and obtaining polyclonal or monoclonal antibodies to the antigens as taught by Frosch.

Applicants respectfully traverse this rejection. As discussed above, Frosch et al. do not teach or suggest methods of obtaining antibodies by providing an Aiolos deregulated animal. In fact, Frosch et al. gives absolutely no indication that deregulation of Aiolos plays a role in increased antibody production. Thus, Applicants respectfully request that the Examiner withdraw this rejection.

Conclusion

Applicant submits that all of the claims are now in condition for allowance, which action is requested. Filed herewith is a check in payment of the excess claims fees required by the above amendments and Petition for Automatic Extension with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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